

**DRUG DELIVERY DEVICE CONTAINING
NEURAMINIDASE INHIBITOR AND AN H1 ANTAGONIST**

INVENTORS:

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FIELD OF THE INVENTION

This invention pertains to a solid oral dosage form containing an antiviral agent and an H1 antagonist, or antihistamine. More particularly, it pertains to dual release osmotic device tablet, which provides a controlled (sustained) release of a neuraminidase inhibitor, such as oseltamivir, zanamivir, peramivir, or other, and a rapid (or immediate) release of an H1 antagonist.

BACKGROUND OF THE INVENTION

Antihistamines, such as H1 histamine receptor antagonists (herein referred to as “H1 antagonists” or “antihistamines”), are used to treat seasonal allergic rhinitis (SAR) and can be used to treat nasal congestion, e.g., stuffed or blocked nasal passages. Epidemiological, biological and clinical studies have shown that viral respiratory infections before the age of 3 years play a crucial role in the later development of rhinitis and asthma. Reduction of their frequency and severity may effect the viral alteration of the pulmonary and immune systems.

A new class of specific anti-influenza agents, the neuraminidase inhibitors, has demonstrated potent inhibition of both influenza A and B viruses. These inhibitors are potent and selective inhibitor of influenza A and B virus neuraminidases. Oseltamivir and zanamivir are approved for treatment of uncomplicated acute illness caused by influenza A or B virus in persons greater than or equal to twelve years of age and who have been symptomatic for no more than two days.

Oseltamivir (TAMIFLU™, OS, GS4104, EN 241104, RO 64-0796, oseltamivir phosphate, an antiviral neuraminidase inhibitor) is used for the treatment of viral infections; however, it does not treat nasal congestion. Oseltamivir is the ethyl ester prodrug of the carbocyclic transition state sialic acid analog RO 64-0802 (GS4071), a

potent and selective inhibitor of influenza A and B virus neuraminidases. Oral oseltamivir was approved for treatment of acute influenza in the United States in 1999. It has demonstrated efficacy both in treating and preventing influenza illness.

Zanamivir (RELENZA™, GG167, 4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid) is a recognized neuraminisase inhibitor useful in the treatment or prevention of influenza virus infection. Zanamivir is generally thought to have poor oral bioavailability due to poor dissolution in the gastrointestinal tract. Khare et al. (*Expert Opin. Pharmacother.* (Mar 2000), 1(3), 367-375) state that the poor oral bioavailability and rapid renal clearance of zanamivir limit its use to inhalation. Cass et al. (*Clin. Pharmacokinet.* (1999), 36 Suppl., 1, 1-11) disclose the results of a comparison study on the pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration. They reported that approximately 90% of the zanamivir was excreted unchanged in the urine and that it was well tolerated at all doses. They also reported that the absolute oral bioavailability of zanamivir was low, averaging 2%, and after intranasal or oral inhaled administration, a median of 10 to 20% of the dose was systemically absorbed, with maximum serum concentrations generally reached within 1 to 2 hours. The median serum half-life ranged between 2.5 and 5.05 hours.

(+/-)-(2S,3R,4R)-2-(trifluoroacetamido)methyl-3-amino-1-(N'-ethyl-N'-isopropylcarbamyl)pyrrolidine-4-carboxylic acid (A-192558, 20e) and 4-(acetylamino)-3-hydroxy-5-nitrobenzoic acid are also recognized neuraminidase inhibitors useful in the treatment or prevention of influenza virus infection.

Peramivir ((1S,2S,3R,4R)-3-[(1S)-(acetylamino)-2-ethylbutyl]-4-[(aminoimino-methyl)amino]-2-hydroxy-cyclopentanecarboxylic acid (RWJ-270201, BCX-1812) is also a recognized neuraminidase inhibitor useful in the treatment or prevention of influenza virus infection.

For antiviral agents to be effective, they must generally be used within 48 hours of the onset of influenza symptoms (Bantia et al. in *Antimicrobial Agents and Chemotherapy*, (Apr. 2001), 45(4), 1162-1167). Antiviral agents reduce the duration of fever and illness by one to two and one-half days and also reduce the severity of some symptoms. Although, oseltamivir reduces the severity of some symptoms, it does not reduce nasal congestion or the production of excessive mucous in the respiratory tract to

the same degree that an H1 histamine receptor antagonist does. Consequently, nasal congestion or the production of excessive mucous in the respiratory tract lingers in patients having been administered oseltamivir.

G. He et al. (*Clin. Pharmacokinet.* (1999 Dec), 37(6), pp. 471-484) report that oral administration of oseltamivir delivers the active antiviral RO 64-0802 to the bloodstream, and thus all sites of influenza infection (lung, nasal mucosa, middle ear) are accessible. They report that the pharmacokinetic profile of oseltamivir is simple and predictable, and that twice-daily treatment results in effective antiviral plasma concentrations over the entire administration interval. After oral administration, oseltamivir is readily absorbed from the gastrointestinal tract and extensively converted to the active metabolite. The absolute bioavailability of the active metabolite from orally administered oseltamivir is reportedly about 80%. The active metabolite is detectable in plasma within 30 minutes and reaches maximal concentrations after 3 to 4 hours with the dosage form used in that study. After peak plasma concentrations are attained, the concentration of the active metabolite declines with an apparent half-life of 6 to 10 hours. Oseltamivir is eliminated primarily by conversion to and renal excretion of the active metabolite. The pharmacokinetic profile of the active metabolite is reportedly linear and dose-proportional, with less than 2-fold accumulation over a dosage range of oseltamivir 50 to 500 mg twice daily. Steady-state plasma concentrations are achieved within 3 days of twice daily administration with the dosage form used in that study. At a dosage of 75mg twice daily, the steady-state plasma trough concentrations of active metabolite remain above the minimum inhibitory concentration for all influenza strains tested. Exposure to the active metabolite at steady state is approximately 25% higher in elderly compared with young individuals; however, no dosage adjustment is necessary. In patients with renal impairment, metabolite clearance decreases linearly with creatinine clearance. A dosage reduction to 75mg once daily is recommended for patients with creatinine clearance <30 ml/min (1.8 L/h). The pharmacokinetics in patients with influenza are reportedly qualitatively similar to those in healthy young adults.

J. Gwaltney (U.S. Patents No. 5,240,694, No. 5,492,689, and No. 5,422,097 discloses COVAM (combined virostatic antimediation) therapy, which includes a method and

compositions for the treatment of the common cold. The method requires the nasal administration of an antiviral composition, optionally containing an antihistamine, and the concurrent oral administration of at least one anti-inflammatory agent. Gwaltney does not disclose a method or composition for the effective treatment of the common cold or other viral infections wherein both the antiviral agent and the antihistamine agent are administered orally. Moreover, Gwaltney does not disclose or suggest a dual release oral solid dosage form containing oseltamivir and an H1 antagonist.

Osmotic devices and other tablet formulations are known for their ability to provide a controlled release of a wide range of drugs. Such osmotic devices and other tablet formulations are disclosed in U.S. Patent No. 4,014,334 to Theeuwes et al., U.S. Patent No. 4,576,604 to Guittard et al., Argentina Patent No. 234,493, U.S. Patent No. 4,673,405 to Guittard et al., U.S. Patent No. 5,558,879 to Chen et al., U.S. Patent No. 4,810,502 to Ayer et al., U.S. Patent No. 4,801,461 to Hamel et al., U.S. Patent No. 5,681,584 to Savastano et al., U.S. Patent No. 3,845,770, U.S. Patent No. 4,008,719 to Theeuwes et al., U.S. Patent No. 4,058,122 to Theeuwes et al., U.S. Patent No. 4,116,241 to Theeuwes et al., U.S. Patent No. 4,160,452 to Theeuwes, U.S. Patent No. 4,256,108 to Theeuwes, and Argentina Patent No. 199,301, the entire disclosures of which are hereby incorporated by reference. In particular, tablet formulations for providing antihistamines are disclosed in U.S. Patent No. 4,650,807 to Findlay *et al.*, and U.S. Patent No. 4,501,893 to Findlay *et al.*, the entire disclosures of which are hereby incorporated by reference.

Dual release conventional sustained release dosage forms are known for the concurrent or sequential administration of two or more drugs by a single unit dosage form. To date, none of the art discloses a dual release oral dosage form that provides a controlled release of an antiviral agent and a rapid release of an H1 antihistamine, or a controlled or sustained release of oseltamivir and a rapid or immediate release of an H1 antihistamine.

While conventional sustained release dosage forms, such as described above, are effective, osmotic devices such as those described by Faour et al. (U.S. 6,004,582), the entire disclosure of which is hereby incorporated by reference, are particularly advantageous for delivering two different dosage forms from a single osmotic device tablet. Faour et al., however, do not disclose osmotic device formulations comprising

slow (controlled/sustained/extended) release neuraminidase inhibitor combined with a rapid (immediate) release H1 antagonist. They also do not disclose osmotic devices that provide the specific formulations, plasma profiles or release profiles for the various different combinations claimed herein. A need remains for improved controlled release formulations of poorly water soluble neuraminidase inhibitors.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a dual release drug delivery system comprising:

a first composition comprising a therapeutically effective amount of a neuraminidase inhibitor and at least one pharmaceutical excipient; and

a different second composition comprising a therapeutically effective amount of an H1 histamine receptor antagonist;

wherein the first composition provides a controlled or sustained release of neuraminidase inhibitor and the second composition provides a rapid or immediate release of an H1 histamine receptor antagonist.

Specific embodiments of the invention include those wherein: 1) the drug delivery system is selected from the group consisting of capsules containing immediate and sustained release granules, capsules containing sustained release granules and one or more immediate release tablets, capsules containing sustained release granules and powder, and extended release film or multi-layer coated tablets; 2) at least 75% of the H1 antagonist is released within about 120 minutes and at least about 70% of the oseltamivir is released within about 24 hours; 3) the first drug composition comprises at least one release rate modifier; 4) the second drug composition comprises an H1 histamine receptor antagonist and at least one pharmaceutical excipient; 5) the first and second drug compositions are in layered arrangement with respect to one another; 6) the second drug composition surrounds the first drug composition; 7) the first drug composition is included in a core and the second drug composition is included in a coat, of one or more coats, surrounding the core; 8) the drug delivery device is a capsule containing the first and second compositions, the first composition is a granulation, and the second composition is a powder, granulation or compressed tablet; and/or 9) the neuraminidase inhibitor is selected from the group consisting of oseltamivir, zanamivir, peramivir, (+/-)-(2S,3R,4R)-2-

(trifluoroacetamido)methyl-3-amino-1-(N'-ethyl-N'-isopropylcarbamyl)pyrrolidine-4-carboxylic acid (A-192558, 20e) and 4-(acetylamino)-3-hydroxy-5-nitrobenzoic acid.

One embodiment of the invention provides an osmotic device comprising:

5 a core comprising a therapeutically effective amount of neuraminidase inhibitor (NA) and at least one osmotic agent or osmopolymer, wherein the core provides a controlled release of NA;

a semipermeable membrane surrounding the core and having a passageway there through; and

10 a drug-containing coat comprising a therapeutically effective amount of an H1 antagonist and surrounding the semipermeable membrane, wherein the external coat provides a rapid release of the H1 antagonist.

Specific embodiments of the osmotic device include those wherein: 1) the osmotic device further comprises an inert water soluble coat interposed the semipermeable membrane and the drug-containing coat; 2) the osmotic device further comprises one or
15 more other coats surrounding the core, wherein the coats are selected from the group consisting of: inert water soluble or water erodible coat, and immediate, rapid, or delayed release coat; 3) the NA is released in a controlled or sustained manner over a period of about 20-24 hours after exposure to an aqueous environment; 4) the H1 antihistamine is released over a period of about 5-120, or 15-120, or 5-60 minutes after exposure to an
20 aqueous environment; 5) osmotic device has an NA dissolution profile and an H1 antagonist dissolution profile as described herein; and/or 6) the NA is selected from the group consisting of oseltamivir, zanamivir, peramivir, (+/-)-(2S,3R,4R)-2-(trifluoroacetamido)methyl-3-amino-1-(N'-ethyl-N'-isopropylcarbamyl)pyrrolidine-4-carboxylic acid (A-192558, 20e) and 4-(acetylamino)-3-hydroxy-5-nitrobenzoic acid.

25 Other specific embodiments include those wherein: 1) a dosage form comprises an effective amount of neuraminidase inhibitor with inherently low oral bioavailability and a bioavailability enhancer present in an amount sufficient to enhance the oral bioavailability of the NA following oral or buccal administration of the dosage form.

30 In some embodiments, the H1 antagonist is selected from the group consisting of acrivastine, astemizol, azelastine, cetirizine, ebastine, epinastine, fexofenadine, desloratadine, loratadine, mizolastine, norastemizol, prometazine and terfenadine.

In other embodiments, the external coat is applied by spray coating rather than by compression coating. By spray coating rather than compression coating the external coat is thinner, and therefore a smaller osmotic device is formed.

Another aspect of the invention provides a method of treating the symptoms of or
5 of ameliorating a viral infection or a common cold. The method comprises the step of administering a dual release dosage form comprising NA and an H1 antagonist, wherein the NA and H1 are released as described herein.

Target therapeutic levels for the H1 antagonist are in the range of about 2 ng to about 700 ng per ml of plasma.

10 Target therapeutic levels for the NA are generally in the range of about 30 to about 200 ng per ml of plasma and, for the active metabolite, in the range of about 250 to about 1300 ng/ml.

Other features, advantages and embodiments of the invention will become apparent to those skilled in the art by the following description, accompanying examples.

15 **BRIEF DESCRIPTION OF THE FIGURES**

The following drawings are part of the present specification and are included to further demonstrate certain aspects of the invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of the specific embodiments presented herein.

20 FIG. 1 depicts a dissolution profile for oseltamivir as it is released in a controlled manner from a dosage form according to Example 1.

FIG. 2 depicts a dissolution profile for fexofenadine as it is released from a dosage form according to Example 1.

25 FIG. 3 depicts a dissolution profile for zanamivir as it is released from a dosage form according to Example 5.

FIG. 4 depicts a dissolution profile for fexofenadine as it is released from a dosage form according to Example 5.

FIG. 5 depicts a dissolution profile for loratadine as it is released from a dosage form according to Example 6.

DETAILED DESCRIPTION OF THE INVENTION

Oseltamivir phosphate (Ro64-0796, GS4104) is a prodrug of oseltamivir carboxylate (Ro64-0802, GS4071), a potent and selective inhibitor of the neuraminidase glycoprotein essential for replication of influenza A and B viruses. Oseltamivir (TAMIFLU®) is available from Roche Pharma™ AG (Switzerland). Alternatively, oseltamivir can be prepared according to the methods described in U.S. Patents No. 5,763,483 to Bischofberger et al and No. 5,866,601 to Lew et al., the disclosures of which are hereby incorporated by reference. Zanamivir is obtainable from Glaxo SmithKline. Alternatively, zanamivir can be prepared and according to the methods described in U.S. Patents No. 6,294,572, No. 5,648,379, and No. 5,360,817. Peramivir is obtainable from Biocryst Pharmaceuticals Inc. Whenever a neuraminidase inhibitor is mentioned herein, all of its chemical forms are included, e.g., enantiomer, diastereomer, salt, racemic, optically pure, and/or salt-free form.

H1 antagonist antihistamines are available from large number of commercial sources. The invention provides for the administration of oseltamivir and H1 antagonists in their free base, free acid, racemic, optically pure, diastereomeric and/or pharmaceutically acceptable salt forms. Suitable H1 antagonist antihistamines include, for example, first generation antihistamines, second generation antihistamines, diphenhydramine, chlorpheniramine, brompheniramine, tripolidine, promethacine, hydroxyzine, pinlamine, dimenhydrinate, acrivastine, azelastine, cetirizine, ebastine, epinastine, fexofenadine, loratadine, mizolastine, norastemizol and prometazine. These drugs are available commercially from a number of pharmaceutical manufacturers.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the therapeutic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of the OS or H1 antagonist. The pharmaceutically acceptable salts include the conventional non-toxic salts, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic,

hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and other known to those of ordinary skill in the pharmaceutical sciences. Lists of suitable salts are found in texts such as *Remington's Pharmaceutical Sciences*, 18th Ed. (Alfonso R. Gennaro, ed.; Mack Publishing Company, Easton, PA, 1990); *Remington: the Science and Practice of Pharmacy* 19th Ed. (Lippincott, Williams & Wilkins, 1995); *Handbook of Pharmaceutical Excipients*, 3rd Ed. (Arthur H. Kibbe, ed.; Amer. Pharmaceutical Assoc., 1999); the *Pharmaceutical Codex: Principles and Practice of Pharmaceutics* 12th Ed. (Walter Lund ed.; Pharmaceutical Press, London, 1994); The United States Pharmacopeia: The National Formulary (United States Pharmacopeial Convention); and *Goodman and Gilman's: the Pharmacological Basis of Therapeutics* (Louis S. Goodman and Lee E. Limbird, eds.; McGraw Hill, 1992), the disclosures of which are hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Figure 1 depicts an OS *in vitro* dissolution profile for the tablets described in Example 1. The release profile of the dual release formulation of the invention will vary from that shown in Figure 1 according to the materials used to form the core and the semipermeable membrane covering the core.

When the formulation is an osmotic device, for example, the release profile can be influenced by the material used to form the semipermeable membrane covering the core, by the material used to form any coating on the semipermeable membrane, by the excipients present in the core, or by the presence of an osmagent in the core. The osmotic device of the invention can have a release profile that generally resembles a pseudo-second order, a second order, a pseudo-third order, or a third order release profile.

Depending upon the particular combination of ingredients used to prepare the osmotic device, the osmotic device will generally provide an expected overall OS release profile resembling a zero order, pseudo-zero order or first order profile. The dissolution profile for oseltamivir for the formulation of Example 1 is generally described as follows:

Time (h)	Maximum released (%)	Minimum released (%)
3	30	5
7	64	27
11	84	48
15	95	62
23	100	74

The OS dissolution profile can also be described as follows:

Time (h)	Average (%)
3	17.5
7	45.5
11	66
15	78.5
23	87

5 All of the tablet formulations of the invention will provide therapeutically effective levels of NA and an H1 antagonist for at least a predetermined period of time. The tablets of the invention will generally provide therapeutically effective amounts of NA for a period of not less than 12 hours and not more than 24 hours, or not less than 10 hours and not more than 32 hours. The controlled release core generally begins to release NA within about
10 0.5-2.0 hours after exposure of the osmotic device to an aqueous solution.

The formulation of Example 1 provides an H1 antagonist (fexofenadine) dissolution profile as depicted in FIG. 2 and an OS dissolution profile as depicted in FIG. 1. The external coating can be an immediately dissolving coating that dissolves in the buccal cavity or a rapidly dissolving coating that dissolves in the buccal cavity, stomach, jejunum or
15 duodenum.

The dissolution profile of the H-1 antagonist is generally described as follows and depicted in FIG. 2.

Time (min)	Minimum Released (%)	Maximum Released (%)
15	24	94
30	40	100
45	60	100
60	80	100
120	<100	100

The rapid release coating of Example 1 releases all of the H1 antagonist within 2 hours after administration and at least 10% of the H1 antagonist within about 10-20 minutes after administration.

- 5 Pharmacokinetic data was obtained for the formulation of Example 1, which includes oseltamivir phosphate (150 mg strength) and fexofenadine hydrochloride (120 mg strength). The following table summarizes the pharmacokinetic data.

Active Agent	T _{max} (h)	AUC _{0-inf} (ng.h/ml)	T _{1/2} (h)
Oseltamivir	3	150-300	5-7
Active metabolite of oseltamivir	8	2500-7500	14
Fexofenadine	1.12-4.0	1716-3306	230-534

- 10 The observed C_{max} for fexofenadine was about 230-534 ng/ml.

- Since zanamivir, and other poorly water soluble or poorly bioavailable neuraminidase inhibitors, are known to possess an inherently low oral bioavailability, a dosage according to the invention can include a bioavailability/bioabsorption enhancer. Examples 5 and 6 detail osmotic device formulations comprising a core, semipermeable
15 membrane surrounding the core, and an H1 antagonist-containing layer surrounding the semipermeable membrane. The core comprises zanamivir and a bioavailability enhancer. FIG. 3 depicts the approximate dissolution profile obtained for zanamivir when the dosage form of Example 5 is placed in solution. The zanamivir is released in a controlled manner over a period of about 16 to 24 hours after exposure to an aqueous environment. The
20 figure includes approximate expected average, maximum and minimum dissolution

profiles for zanamivir for this exemplary osmotic device. The approximate release profiles can be expressed as follows:

Sampling time (hrs)	Average (%)	STD \pm (%)	RANGE (%)	
			MAX	MIN
0	0	0	0	0
4	17	5.0	35	5
8	45	5.0	65	25
12	65	6.0	87	48
16	77	5.0	99	60
24	90	4.0	100	70

Each of the average, maximum and minimum values are subject to the standard deviation (STD) indicated above. The release of zanamivir follows a sigmoidal, first order, pseudo-first order, zero order or pseudo-zero order release profile.

The release of fexofenadine (FEX) from the dosage form of Example 5 is depicted in FIG. 4. FEX is released substantially completely throughout or within a period of about two hours or less after the osmotic device is exposed to an aqueous environment. FEX can be released over the two hour period or a shorter period. It is released rapidly when its release finally starts; however, initiation of release is optionally delayed by a first lag time. The figure includes approximate mean, maximum and minimum release profiles that can be expressed as follows.

Sampling time (min)	0	10	15	30	45
Mean released (%)	0	50	65	85	92
Minimum released (%)	0	35	50	75	80
Maximum released (%)	0	70	85	100	105

The osmotic device of Example 6 is very similar to that of Example 5 with the key exception that loratadine, instead of fexofenadine, is used as the H1 receptor antagonist. FIG. 5 depicts the approximate average, maximum and minimum release profiles of loratadine from this exemplary osmotic device. Those release profiles can be summarized as follows.

Sampling time (min)	Average (%)	STD \pm (%)	RANGE (%)	
			MAX	MIN
0	0	0	0	0
15	35	8.5	15	55
30	75	5.6	60	93
45	85	7.8	70	100
60	90	8.0	75	100

Each of the average, maximum and minimum values are subject to the standard deviation (STD) indicated above. The release of loratadine (the H1 antagonist) can occur in a burst (within zero to five minutes), over a short period of time (within 5 to 120 minutes) or throughout a period of less than or about 2 hours or 1 hour.

As used herein, the term bioavailability enhancer (bioabsorption enhancer) refers to an agent or combination of agents that enhance absorption of a NA inhibitor of the invention across the lining of the gastrointestinal tract. Many of the known bioavailability enhancers can be used for this purpose. Examples 5 and 6 includes vitamin E TPGS as a suitable bioabsorption enhancer for zanamivir. Vitamin E TPGS, d- α -tocopheryl polyethylene glycol 1000 succinate, is a water-soluble derivative of natural-source vitamin E available from Eastman Chemical Company. Other suitable enhancers include acetylated monoglyceride, citric acid, malic acid, ascorbic acid, fumaric acid, caproic acid, caprylic acid, cholic acid, glycocholic acid, sodium cholate, sodium lauryl sulfate, palmitoyl carnitin, other oral bioavailability-enhancing materials known to those of ordinary skill in the art, or mixtures thereof. Depending upon the NA inhibitor used a particular bioavailability/bioabsorption enhancer may provide optimal performance. The ratio of bioavailability enhancer to NA inhibitor can be adjusted as needed according to the transport enhancement of the NA inhibitor across human cells such as skin fibroblasts and the human derived intestinal cell line Caco-2 in culture (*Am. J. Clin.Nutr.*, 1988, 48: 605-11), and/or the oral bioavailability of the NA inhibitor in dogs.

Those of ordinary skill in the art will appreciate that the particular amounts of NA inhibitor and H1 antagonist used in the osmotic device will vary according to, among other things, the desired pharmacokinetic behavior in a subject. The NA inhibitor is present in the core in an amount ranging from 75-800 mg and, the H1 antagonist in the drug-containing water soluble coating is present in an amount ranging from 2.5-180 mg.

A water-soluble coating, inert or drug-containing, will generally comprise an inert and non-toxic material which is at least partially, and optionally substantially completely, soluble or erodible in an environment of use. Selection of materials suitable for the inert or drug-containing water soluble coatings will depend upon the desired release rate of drug from the drug-containing coating and upon the desired separation of drug delivery from the core versus the drug-containing coating. A rapidly dissolving coat will be soluble in the buccal cavity and/or upper GI tract, such as the stomach, duodenum, jejunum or upper small intestines. Exemplary materials are disclosed in U.S. Patents No. 4,576,604 to Guittard et al. and No. 4,673,405 to Guittard et al., and No. 6,004,582 to Faour et al. and the text *Pharmaceutical Dosage Forms: Tablets Volume I, 2nd Edition*. (A. Lieberman, ed. 1989, Marcel Dekker, Inc.), the relevant disclosures of which are hereby incorporated by reference. In some embodiments, the rapidly dissolving coat will be soluble in saliva, gastric juices, or acidic fluids.

Materials which are suitable for making the water soluble or erodible coatings of the invention include, by way of example and without limitation, water soluble polysaccharide gums such as carrageenan, fucoidan, gum ghatti, tragacanth, arabinogalactan, pectin, and xanthan; water-soluble salts of polysaccharide gums such as sodium alginate, sodium tragacanthin, and sodium gum ghattate; water-soluble hydroxyalkylcellulose wherein the alkyl member is straight or branched of 1 to 7 carbons such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose; synthetic water-soluble cellulose-based lamina formers such as methyl cellulose and its hydroxyalkyl methylcellulose cellulose derivatives such as a member selected from the group consisting of hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, and hydroxybutyl methylcellulose; croscarmellose sodium; other cellulose polymers such as sodium carboxymethylcellulose; and other materials known to those of ordinary skill in the art. Other lamina forming materials that can be used for this purpose include poly(vinylpyrrolidone), polyvinylalcohol, polyethylene oxide, a blend of gelatin and polyvinyl-pyrrolidone, gelatin, glucose, saccharides, povidone, copovidone, poly(vinylpyrrolidone)-poly(vinyl acetate) copolymer. The water soluble coating can comprise other pharmaceutical excipients that do or do not alter the way in which the

water soluble coating behaves. The artisan of ordinary skill will recognize that the above-noted materials include film forming polymers.

Other materials which can be used in the water soluble or erodible coatings include hydroxypropylcellulose, microcrystalline cellulose (MCC, Avicel™ from FMC Corp.),
5 poly(ethylene-vinyl acetate) (60:40) copolymer (EVAC from Aldrich Chemical Co.), 2-hydroxyethylmethacrylate (HEMA), MMA, terpolymers of HEMA:MMA:MA synthesized in the presence of N,N'-bis(methacryloyloxyethyloxycarbonylamino)-azobenzene, azopolymers, enteric coated timed release system (Time Clock® from Pharmaceutical Profiles, Ltd., UK) and calcium pectinate can be included in the water soluble coat.

10 The inert water soluble or water erodible coat covering the semipermeable wall and blocking the passageway is made of synthetic or natural material which, through selective dissolution or erosion shall allow the passageway to be unblocked thus allowing the process of osmotic delivery to start. This slow or fast dissolving water soluble coat can be impermeable to a first external fluid, while being soluble in a second external fluid. This
15 property can help to achieve a controlled and selective release of the active compound in the nucleus.

In some embodiments, the inert water soluble or erodible coat will be insoluble in the fluid of a first environment of use, such as gastric juices, acidic fluids, or polar liquids, and soluble or erodible in the fluid of a second environment of use, such as intestinal
20 juices, substantially pH neutral or basic fluids, or apolar liquids. A wide variety of other polymeric materials are known to possess these various solubility properties and can be included in the water soluble coat. Such other polymeric materials include, by way of example and without limitation, cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate)phthalate (PVAP), hydroxypropyl methylcellulose
25 phthalate (HP), poly(methacrylate ethylacrylate) (1:1) copolymer (MA-EA), poly(methacrylate methylmethacrylate) (1:1) copolymer (MA-MMA), poly(methacrylate methylmethacrylate) (1:2) copolymer, Eudragit™ L-30-D (MA-EA, 1:1), Eudragit™ L-100-55 (MA-EA, 1:1), hydroxypropylmethylcellulose acetate succinate (HPMCAS), Coateric™ (PVAP), Aquateric™ (CAP), AQOAT™ (HPMCAS) and combinations
30 thereof. The water soluble coat can also comprise dissolution aids, stability modifiers, and bioabsorption enhancers.

An optional polymeric material for use in the inert water soluble or erodible coat includes enteric materials that resist the action of gastric fluid avoiding permeation through the semipermeable wall while one or more of the materials in the core are solubilized in the intestinal tract thereby allowing delivery of a drug in the core by osmotic pumping to begin. A material that easily adapts to this kind of requirement is a poly(vinylpyrrolidone)-vinyl acetate copolymer, such as the material supplied by BASF under its Kollidon VA64 trademark, mixed with magnesium stearate and other similar excipients. The water soluble coat can also comprise povidone, which is supplied by BASF under its Kollidon K 30 trademark, and hydroxypropyl methylcellulose, which is supplied by Dow under its Methocel E-15 trademark. The materials can be prepared in solutions having different concentrations of polymer according to the desired solution viscosity. For example, a 10% P/V aqueous solution of Kollidon™ K 30 has a viscosity of about 5.5-8.5 cps at 20.degree. C., and a 2% P/V aqueous solution of Methocel™ E-15 has a viscosity of about 13-18 cps at 20.degree. C.

The inert water soluble or water erodible coat can also comprise other suitable materials which are substantially resistant to gastric juices and which will promote either enteric or colonic release. For this purpose, the inert water soluble coat can comprise one or more materials that do not dissolve, disintegrate, or change their structure in the stomach and during the period of time that the osmotic device resides in the stomach.

Representative materials that keep their integrity in the stomach can comprise a member selected from the group consisting of (a) keratin, keratin sandarac-tolu, salol (phenyl salicylate), salol beta-naphthylbenzoate and acetotannin, salol with balsam of Peru, salol with tolu, salol with gum mastic, salol and stearic acid, and salol and shellac; (b) a member selected from the group consisting of formalized protein, formalized gelatin, and formalized cross-linked gelatin and exchange resins; (c) a member selected from the group consisting of myristic acid-hydrogenated castor oil-cholesterol, stearic acid-mutton tallow, stearic acid-balsam of tolu, and stearic acid-castor oil; (d) a member selected from the group consisting of shellac, ammoniated shellac, ammoniated shellac-salol, shellac-wool fat, shellac-acetyl alcohol, shellac-stearic acid-balsam of tolu, and shellac n-butyl stearate; (e) a member selected from the group consisting of abietic acid, methyl abictate, benzoin, balsam of tolu, sandarac, mastic with tolu, and mastic with tolu, and mastic with acetyl

alcohol; (f) acrylic resins represented by anionic polymers synthesized from methacrylate acid and methacrylic acid methyl ester, copolymeric acrylic resins of methacrylic and methacrylic acid and methacrylic acid alkyl esters, copolymers of alkacrylic acid and alkacrylic acid alkyl esters, acrylic resins such as dimethylaminoethylmethacrylate-
5 butylmethacrylate-methylmethacrylate copolymer of 150,000 molecular weight, methacrylic acid-methylmethacrylate 50:50 copolymer of 135,000 molecular weight, methacrylic acid-methylmethacrylate-30:70-copolymer of 135,000 mol. wt., methacrylic acid-dimethylaminoethyl-methacrylate-ethylacrylate of 750,000 mol. wt., methacrylic acid-methylmethacrylate-ethylacrylate of 1,000,000 mol. wt., and ethylacrylate-
10 methylmethacrylate-ethylacrylate of 550,000 mol. wt; and, (g) an enteric composition comprising a member selected from the group consisting of cellulose acetyl phthalate, cellulose diacetyl phthalate, cellulose triacetyl phthalate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate, methylcellulose phthalate, cellulose ester-ether
15 phthalate, hydroxypropyl cellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, calcium salt of cellulose acetate phthalate, ammonium salt of hydroxypropyl methylcellulose phthalate, cellulose acetate hexahydrophthalate, hydroxypropyl methylcellulose hexahydrophthalate, polyvinyl acetate phthalate diethyl phthalate, dibutyl phthalate, dialkyl phthalate wherein the alkyl comprises
20 from 1 to 7 straight and branched alkyl groups, aryl phthalates, and other materials known to one of ordinary skill in the art.

The semipermeable membrane of the osmotic device is formed of a material that is substantially permeable to the passage of fluid from the environment of use to the core and substantially impermeable to the passage of active agent from the core. Many common
25 materials known by those of ordinary skill in the art are suitable for this purpose. Exemplary materials are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, cellulose acetate butyrate and ethylcellulose. cellulose esters, cellulose ethers and cellulose
30 esters-ethers. A preferred semipermeable membrane material is cellulose acetate, commercially available from Eastman Chemical Products. The semipermeable membrane

can also contain flux enhancing agents which increase the volume of fluid imbibed into the core, such as sugar, mannitol, sucrose, sorbitol, sodium chloride, potassium chloride, polyethylene glycol (weight av. molecular weight 380-3700), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose and mixtures thereof. A preferred
5 flux enhancer is PEG 400. The semipermeable membrane can also contain plasticizers. Suitable plasticizers for manufacturing the semipermeable membrane include sebacate, dibutylsebacate, adipate, azelate, enzoate, citrate, triethylcitrate, tributylcitrate, glyceroltributyrate, acetyltributylcitrate, acetyltriethylcitrate, stearate, isoeubacate, citric acid esters, diethyloxalate, acetylated monoglyceride, oils such as olive, sesame and rape
10 seed oil, and the like. A preferred plasticizer is triacetin. The ratio of the components and the thickness of the semipermeable membrane can be varied to alter permeability and ultimately the release profile of the osmotic device. Many suitable polymers, include those disclosed in Argentine Patent No. 199,301 U.S. patent No. 4,814,183 and other references cited herein, the disclosures of which are hereby incorporated by reference.

15 Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di and tricellulose alkanylates, mono, di and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of
20 32 to 39.8%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose triacetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%; and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content
25 of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%; a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose triocanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose diocanoate, cellulose
30 dipentale, and the like. Additional semipermeable polymers include acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate for use in

environments having a low pH, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semipermeable polyamides, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, cross-linked selectively semipermeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Patents
5 No. 3,173,876, No. 3,276,586, No. 3,541,005, No. 3,541,006, and No. 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; lightly cross-linked polystyrene derivatives; cross-linked poly(sodium styrene sulfonate), cross-linked poly(vinylbenzyltrimethyl ammonium chloride), semipermeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-1} (cc.mil/cm².hr.atm)
10 expressed as per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. These and others polymers are disclosed in U.S. Patents No. 3,845,770, No. 3,916,899, No. 4,765,989 and No. 4,160,020; and in *Handbook of Common Polymers* (Scott, J. R. and Roff, W. J., eds.; 1971; CRC Press, Cleveland, Ohio).

The osmotic device of the invention comprises at least one passageway (pore, hole,
15 or aperture) that communicates the exterior of the semipermeable wall with the core of the device. The passageway can be formed according to any of the known methods of forming passageways in a semipermeable membrane. Such methods include, for example, 1) drilling a hole through the semipermeable membrane with a bit or laser; 2) including a water soluble material within the composition that forms the semipermeable membrane
20 such that a pore forms when the osmotic device is in an aqueous environment of use; 3) punching a hole through the semipermeable membrane; or 4) employing a tablet punch having a pin to punch a hole through the semipermeable lamina. The passageway can pass through the semipermeable wall and one or more of any other lamina coated onto the semipermeable membrane or between the semipermeable membrane and the core. The
25 passageway(s) can be shaped as desired. In some embodiments, the passageway is laser drilled and is shaped as an oval, ellipse, slot, slit, cross or circle.

Methods of forming passageways in semipermeable membranes of osmotic devices are disclosed in U.S. Patents No. 4,088,864 to Theeuwes et al., No. 4,016,880 to Theeuwes et al., No. 3,916,899 to Theeuwes et al., No. 4,285,987 to Ayer et al., No. 4,783,337 to
30 Wong et al., No. 5,558,879 to Chen et al., No. 4,801,461 to Hamel et al., and No.

3,845,770 to Theeuwes et al., the disclosures of which are hereby incorporated by reference.

The core of the tablet of the present invention will comprise NA, at least one pharmaceutically acceptable excipient and optionally one or more other materials.

5 Generally, the tablet formulations will comprise about 0.1-99.9% by weight of NA in the uncoated tablet core. Acceptable ranges may vary according to the desired therapeutic response, the tablet size, the amount and type of excipients used in the core of the device, the H1 antagonist used and the intended use of the osmotic device.

When the controlled release tablet is an osmotic device, osmotically effective
10 solutes, osmotic agents or osmagents can be added. These osmagents can aid in either the suspension or dissolution of the NA in the core. Exemplary osmagents include organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium
15 lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials which are widely known in the art. Osmagents can also be incorporated to the core of the osmotic device to control the release of NA therefrom. U.S. Patent No. 4,077,407 to Theeuwes et al., the entire disclosure of which is hereby incorporated by reference, discloses suitable
20 osmagents.

The tablets of the invention can also comprise adsorbents, acidifying agent, alkalizing agent, antioxidants, buffering agents, colorants, flavorants, sweetening agents, tablet antiadherents, tablet binders, tablet and capsule diluents, tablet direct compression excipients, tablet disintegrants, tablet glidants, tablet lubricants, tablet or capsule opaquants,
25 complexing agent, preservative and/or tablet polishing agents.

A used herein, a complexing agent is an agent that complexes metal ions. Exemplary complexing agents include EDTA disodium, edetate, pentates and others known to those of ordinary skill in the art.

As used herein, the term "acidifying agent" is intended to mean a compound used
30 to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, amino acid, citric acid, fumaric acid and other

alpha hydroxy acids, such as hydrochloric acid, ascorbic acid, and nitric acid and others known to those of ordinary skill in the art.

As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, and triethylamine and others known to those of ordinary skill in the art.

As used herein, the term "adsorbent" is intended to mean an agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means. Such compounds include, by way of example and without limitation, powdered and activated charcoal and other materials known to one of ordinary skill in the art.

As used herein, the term "antioxidant" is intended to mean an agent which inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process. Such compounds include, by way of example and without limitation, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate and sodium metabisulfite and other materials known to one of ordinary skill in the art.

As used herein, the term "buffering agent" is intended to mean a compound used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dihydrate and other materials known to one of ordinary skill in the art.

As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol and sucrose and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet antiadherents" is intended to mean agents which prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production. Such compounds include, by way of example and without

limitation, magnesium stearate, talc, calcium stearate, glyceryl behenate, PEG, hydrogenated vegetable oil, mineral oil, stearic acid and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet binders" is intended to mean substances used to cause adhesion of powder particles in table granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, carboxymethylcellulose sodium, poly(vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch and other materials known to one of ordinary skill in the art.

As used herein, a preservative is an agent or combination of agents that inhibits, reduces or eliminates bacterial growth in a pharmaceutical dosage form. Exemplary preservatives includes Nipagin, Nipazol, Isopropyl alcohol and a combination thereof.

When needed, binders may also be included in the tablets. Exemplary binders include acacia, tragacanth, gelatin, starch, cellulose materials such as methyl cellulose and sodium carboxy methyl cellulose, alginic acids and salts thereof, polyethylene glycol, guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, gelatin, cellulose in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, polypropylene glycol, polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, polyethylene oxide, combinations thereof and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet and capsule diluent" or "fillers" is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, lactose, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, and starch and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet direct compression excipient" is intended to mean a compound used in direct compression tablet formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate (e.g., Datab) and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet glidant" is intended to mean agents used in tablet and capsule formulations to promote flowability of the granulation. Such compounds include, by way of example and without limitation, colloidal silica, cornstarch, talc, calcium silicate, magnesium silicate, colloidal silicon, silicon hydrogel and other materials known to one of
5 ordinary skill in the art.

As used herein, the term "tablet lubricant" is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, and zinc stearate and other materials known to one of ordinary skill in the art.

10 As used herein, the term "tablet/capsule opaquant" is intended to mean a compound used to render a capsule or a tablet coating opaque. May be used alone or in combination with a colorant. Such compounds include, by way of example and without limitation, titanium dioxide, talc and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet polishing agent" is intended to mean a compound
15 used to impart an attractive sheen to coated tablets. Such compounds include, by way of example and without limitation, carnauba wax, white wax and other materials known to one of ordinary skill in the art.

As used herein, the term "tablet disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which
20 are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starches thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose(e.g., Avicel), carboxymethylcellulose calcium, cellulose polyacrilin potassium (e.g., Amberlite), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya,
25 pectin, tragacanth; crospovidone and other materials known to one of ordinary skill in the art.

As used herein, the term "colorant" is intended to mean a compound used to impart color to solid (e.g., tablets) pharmaceutical preparations. Such compounds include, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel,
30 and ferric oxide, red, other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, and other

materials known to one of ordinary skill in the art. The amount of coloring agent used will vary as desired.

As used herein, the term "flavorant" is intended to mean a compound used to impart a pleasant flavor and often odor to a pharmaceutical preparation. Exemplary flavoring agents or flavorants include synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may also include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Other useful flavors include vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors which have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors will be present in any amount as desired by those of ordinary skill in the art. Particularly flavors are the grape and cherry flavors and citrus flavors such as orange.

The present tablets can also employ one or more commonly known surface active agents or cosolvents that improve wetting or disintegration of the tablet core or layers.

Plasticizers can also be included in the tablets to modify the properties and characteristics of the polymers used in the coats or core of the tablets. As used herein, the term "plasticizer" includes all compounds capable of plasticizing or softening a polymer or binder used in invention. The plasticizer should be able to lower the melting temperature or glass transition temperature (softening point temperature) of the polymer or binder. Plasticizers, such as low molecular weight PEG, generally broaden the average molecular weight of a polymer in which they are included thereby lowering its glass transition temperature or softening point. Plasticizers also generally reduce the viscosity of a polymer. It is possible the plasticizer will impart some particularly advantageous physical properties to the osmotic device of the invention.

Plasticizers useful in the invention can include, by way of example and without limitation, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers,

glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin. Such plasticizers can also include ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutylsebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co. It is also contemplated and within the scope of the invention, that a combination of plasticizers may be used in the present formulation. The PEG based plasticizers are available commercially or can be made by a variety of methods, such as disclosed in *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J.M. Harris, Ed.; Plenum Press, NY) the disclosure of which is hereby incorporated by reference.

The tablets of the invention can also include oils, for example, fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids, such as oleic acid, stearic acid and isotearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. It can also be mixed with alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; with glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; with ethers, such as poly(ethyleneglycol) 450, with petroleum hydrocarbons, such as mineral oil and petrolatum; with water, or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

Soaps and synthetic detergents may be employed as surfactants and as vehicles for detergent compositions. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene)

copolymers; and amphoteric detergents, for example, alkyl β -aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

Various other components, not otherwise listed above, can be added to the present formulation for optimization of a desired active agent release profile including, by way of example and without limitation, glycerylmonostearate, nylon, cellulose acetate butyrate, d, l-poly(lactic acid), 1,6 - hexanediamine, diethylenetriamine, starches, derivatized starches, acetylated monoglycerides, gelatin coacervates, poly (styrene - maleic acid) copolymer, glycowax, castor wax, stearyl alcohol, glycerol palmitostearate, poly(ethylene), poly(vinyl acetate), poly(vinyl chloride), 1,3 - butylene-glycoldimethacrylate, ethyleneglycol-dimethacrylate and methacrylate hydrogels.

It should be understood, that compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

By the term "effective amount", it is understood that, with respect to, for example, pharmaceuticals, a therapeutically effective amount is contemplated. A therapeutically effective amount is the amount or quantity of NA, or H1 antagonist, which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient.

The tablets of the invention can assume any shape or form known in the art of pharmaceutical sciences. The device of the invention can be a pill, sphere, tablet, bar, plate, paraboloid of revolution, ellipsoid of revolution or the like. The tablets can also include surface markings, cuttings, grooves, letters and/or numerals for the purposes of decoration, identification and/or other purposes.

The tablets of the invention can be prepared according to the methods disclosed herein or those well known in the art, more specifically according to the methods disclosed in the disclosure incorporated herein by reference. For example, according to one manufacturing technique, NA and excipients that comprise the core are mixed in solid, semisolid or gelatinous form, then moistened and sieved through a specified screen to obtain granules. The granules are then dried in a dryer and compressed, for example, by

punching to form uncoated cores. The compressed and uncoated cores are then covered with a semipermeable membrane. Subsequently, the semipermeable membrane surrounding the core should be perforated with, for example, laser equipment. Finally, an external coat containing the H1 antagonist is applied to the semipermeable membrane.

5 The external coat can be applied as a compression coating, but it is generally applied as a sprayed coating. The sprayed coating is thinner and lighter than the compression coating, and an osmotic device including the sprayed on external coating is, therefore, smaller than a similar osmotic device having a compression coat. Moreover, the use of a sprayed-on drug-containing water soluble coating permits the loading of higher
10 amounts of drug than the use of a compression-coated drug-containing water soluble coating. A smaller size osmotic device generally results in increased patient compliance in taking the osmotic device and is therefore advantageous.

 The tablets of the invention can be coated with a finish coat as is commonly done in the art to provide the desired shine, color, taste or other aesthetic characteristics.
15 Materials suitable for preparing the finish coat are well known in the art and found in the disclosures of many of the references cited and incorporated by reference herein.

 The method of ameliorating a viral infection or of eliminating and/or reducing severity of congestion or mucous-related symptoms associated with a viral infection comprises the step of administering a solid oral dosage form comprising oseltamivir and
20 an H1 antagonist to a patient, wherein the NA is provided at a controlled rate for an extended period of time and the H1 antagonist is provided rapidly, i.e., within a short period of time, after administration. The method includes the steps of providing therapeutically effective levels of both drugs. This combination treatment method will reduce the severity of congestion related symptoms associated with a viral infection (such
25 as influenza or the common cold) more so than treatment with oseltamivir alone.

 The advantages of the present system over known systems for administering oseltamivir in combination with an H1 antagonist is improved therapeutic benefit, control of or amelioration of the symptoms associated with viral infection, simplified manufacturing, and/or increased patient compliance.

30 As used herein, the terms "controlled", "extended", "retarded" or "sustained" release are generally used interchangeably and indicate a release profile wherein the active

agent is released slowly and about continually over a lengthened period of time. The intended period of time is as described herein.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention.

- 5 The methods described herein can be followed to prepare dosage forms according to the invention.

EXAMPLE 1

The following general method was used to prepare osmotic devices according to the invention. In one embodiment, a large scale batch of oseltamivir phosphate (150 mg strength, OS-Ph) and fexofenadine hydrochloride (120 mg strength) osmotic device tablets
10 was prepared by mixing 197.00 g of OS-Ph, 145.00 g of mannitol (osmagent), and 40.00 g of povidone (binder). The mixture was wetted with a blend of 46.00 ml of alcohol 96°, 2.30 g of PEG 400 (plasticizer) and 10.00 g of PEG 6000. The blend was granulated and dried at 40 – 50° C for 4 hours; then, it was screened and mixed with 2.00 g of colloidal
15 silicon dioxide (glidant). The blend was mixed to homogeneity and 3.70 g of magnesium stearate (lubricant) was added. The final blend was tableted using biconcave, 10.00 -mm diameter punches to form uncoated cores. Core weight: 400.0 mg; hardness from 8 to 12 kp.

A first composition to cover the uncoated cores was prepared as follows: 32.30 g of
20 cellulose acetate (cellulose ester) and 1.7 g of PEG 400 (plasticizer) was added to 1310.0 ml of a blend of acetone (710 ml) and methanol (300 ml) organic solvents. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed approximately 34.0 mg. A 0.50-mm hole was laser drilled through the coating in one face of the tablet.

25 The second coating was prepared by mixing 1.95 g of copolyvidone (water soluble polymer), 1.75g of titanium dioxide (opaquant), 6.25 g of talc and 50.00 mg of Aluminum Lake Ponceau Red (colorant) in Isopropyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed approximately 10 mg.

30 The third coating was prepared by mixing 120.00 g of fexofenadine hydrochloride, 150.0 g of microcrystalline cellulose (disintegrant), 100.0 g of lactose monohydrate, 35.00

g of cornstarch, 32.00 g of povidone (film forming polymer). The mixture was wetted and mixed with 130.00 ml of purified water, 9.00 g of PEG 400 (plasticizer), and 30.00 g of PEG 6000. The blend was granulated and dried at 40-50°C for 3 hours. The granulation was then sieved and mixed with 1.00 g of colloidal silicon dioxide (glidant). This blend
5 was mixed to homogeneity and 6.00 g of magnesium stearate was mixed in as well. The final blend was compressed about the second coating using 14.00 mm diameter punches to form tablets weighing about 483.0 mg having a hardness of about 7-12 kP.

The final coating was prepared by mixing 12.10 g of HPMC 2910 (film forming polymer), 3.42 g of PEG 6000 (plasticizer) and 4.48 g of titanium dioxide (opaquant) in a
10 mixture of methylene chloride and alcohol (96°) (70:30, v/v). This polymer mixture was sprayed onto the drug-containing third coating in a conventional pan coater to form an outer coating weighing about 20 mg.

The osmagent, diluent, binder, plasticizer, glidant, disintegrant, lubricant, cellulose ester, water soluble polymer, opaquant, and film forming polymer used in the present
15 formulation were selected from the respective groups of ingredients set forth herein. The organic solvents used herein can include, for example, ethanol, methanol, isopropanol, methylene chloride, and others typically used in the pharmaceutical sciences.

EXAMPLE 2

The following general method was used to prepare osmotic devices according to
20 the invention. In one embodiment, a large scale batch of oseltamivir phosphate (150 mg strength, OS-Ph) and loratadine (10 mg strength) osmotic device tablets was prepared by mixing 197.00 g of OS-Ph, 55.00 g of sodium chloride (osmagent), and 40.00 g of povidone (binder). The mixture was wetted with a blend of 46.00 ml of alcohol 96°, 2.30 g of PEG 400 (plasticizer) and 10.00 g of PEG 6000. The blend was granulated and dried
25 at 40 – 50° C for 4 hours; then, it was screened and mixed with 2.00 g of colloidal silicon dioxide (glidant). The blend was mixed to homogeneity and 3.70 g of magnesium stearate (lubricant) was added. The final blend was tabletted using biconcave 10.00 mm diameter punches to form uncoated cores. Core weight: 310.0 mg; hardness from 8 to 12 kp.

A first composition to cover the uncoated cores was prepared as follows: 32.30 g of
30 cellulose acetate (cellulose ester) and 1.7 g of PEG 400 (plasticizer) was added to 1310.0 ml of a blend of acetone (710 ml) and methanol (300 ml) organic solvents. This polymer

mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed approximately 28.0 mg. A 0.50-mm hole was laser drilled through the coating in one face of the tablet.

The second coating was prepared by mixing 1.95 g of copolyvidone (water soluble polymer), 1.75g of titanium dioxide (opaquant), 6.25 g of talc and 50.00 mg of Aluminum Lake Ponceau Red (colorant) in Isopropyl Alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed approximately 12 mg.

The third coating was prepared by mixing 10.00 g of loratadine, 23.40 g of HPMC 2910 (film-forming polymer), 5.40 g of PEG 6000 (plasticizer), 9.60 g of crospovidone (binder), and 0.60 g of colloidal silicon dioxide (glidant) in purified water. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which coating weighed approximately 49.0 mg.

The final coating was prepared by mixing 12.10 g of HPMC 2910 (film forming polymer), 3.42 g of PEG 6000 (plasticizer) and 4.48 g of titanium dioxide (opaquant) in a mixture of methylene chloride and alcohol (96°) (70:30, v/v). This polymer mixture was sprayed onto the drug-containing third coating in a conventional pan coater to form an outer coating weighing about 15 mg.

The osmagent, diluent, binder, plasticizer, glidant, lubricant, cellulose ester, water soluble polymer (disintegrant), opaquant, and film forming polymer used in the present formulation were selected from the respective groups of ingredients set forth above. The organic solvents used herein can include, for example, ethanol, methanol, isopropanol, methylene chloride, and others typically used in the pharmaceutical sciences.

EXAMPLE 3

The following procedure was used to prepare capsules consisting essentially of oseltamivir-containing sustained release granules and loratadine-containing immediate release tablets. The capsules made according to this procedure included the following ingredients in the approximate amounts indicated.

Ingredient	Amount (mg)
Oseltamivir Phosphate	150.00
Loratadine	10.00
Ethylcellulose Aqueous Dispersion	15.00
Acetylated Monoglyceride	8.40
Sodium Croscarmellose	11.25
Glyceryl Monostearate (Myvaplex 600 P)	105.00
Microcrystalline Cellulose PH 301	81.00
Magnesium Stearate	2.00
Dicalcium Phosphate	25.75
Purified Water	5.00 ml

The capsules were made as follows. Oseltamivir Phosphate and Myvaplex 600 P were thoroughly mixed and melt extruded through a USP 12-mesh screen. The extrudate was spheronized and sieved through a USP 12-mesh screen. The spheronized granules were coated with an aqueous dispersion of ethylcellulose containing acetylated monoglyceride (plasticizer).

Dicalcium phosphate, loratadine, and microcrystalline cellulose PH301 were placed in a mixer and mixed for six minutes. Magnesium stearate was added to the mixture and the mixture was sieved through a USP 60-mesh screen to form a composition that was compressed into tablets having an approximate weight of about 130 milligrams each.

Size 000 capsules were filled with a loratadine-containing tablet and the desired quantity of oseltamivir granules as required to form the required dose.

EXAMPLE 4

The following procedure was used to prepare capsules consisting essentially of oseltamivir-containing sustained release granules and fexofenadine-containing immediate release capsules. The capsules made according to this procedure included the following ingredients in the approximate amounts indicated.

Ingredient	Amount (mg)
Oseltamivir Phosphate	150.00
Fexofenadine	120.00
Ethylcellulose Aqueous Dispersion	15.00
Acetylated Monoglyceride	8.40
Glyceryl Monostearate (Myvaplex 600 P)	105.00

Ingredient	Amount (mg)
Microcrystalline Cellulose PH 101	51.00
Gelatin	3.00
Yellow Lake N°10 D&C	5.60
Magnesium Stearate	2.00
Purified Water	5.00 ml

The capsules were made as follows. Oseltamivir Phosphate and Myvaplex 600 P were thoroughly mixed and melt extruded through a USP 12-mesh screen. The extrudate was spheronized and sieved through a USP 12-mesh screen. The spheronized granules were coated with an aqueous dispersion of ethylcellulose containing acetylated monoglyceride (plasticizer).

Fexofenadine and microcrystalline cellulose PH101 were placed in a mixer and mixed for six minutes and granulated with a solution of gelatin in water containing the colorant. The mass was extruded through a USP 12-mesh screen and spheronized. The extrudate was tray dried.

The oseltamivir-containing granules were mixed with the fexofenadine-containing granules at the desired ratio. Magnesium stearate was mixed with the mixture of granules to form a drug-containing composition that was filled into size 000 capsules as required to form the required dose.

EXAMPLE 5

The following procedure is used to prepare a multi-layered osmotic device consisting essentially of zanamivir (200, 400 and 800 mg strength) in controlled release form in the core and fexofenadine HCl (120 mg strength) in immediate/rapid release form in a layer surrounding the coated core. The osmotic device made according to this procedure includes the following ingredients in the approximate amounts indicated.

Ingredient	Amount (mg)		
Zanamivir Strength⇒	200.00	400.00	800.00
Fexofenadine HCl Strength⇒	120.00	120.00	120.00
CORE			
Zanamivir	200.00	400.00	800.00
Sodium Chloride	49.00	50.40	53.20
Polysorbate 20	1.00	1.50	2.00
Povidone	7.00	10.00	20.00

Ingredient	Amount (mg)		
Hydroxypropyl methylcellulose 2208	5.00	6.00	10.00
Polyethylene Oxide 205 NF	35.00	42.00	49.00
Cellulose Microcrystalline	56.00	47.50	10.00
Vitamin E TPGS	36.60	39.00	43.80
Colloidal Silicon Dioxide	2.00	3.00	4.00
Magnesium Stearate	4.00	5.00	8.00
COATING A			
Cellulose Acetate 398	19.00	23.75	28.50
Polyethylene Glycol 400	1.00	1.25	1.50
Acetone	400.00	500.00	600.00
COATING B			
Fexofenadine Hydrochloride	120.00	120.00	120.00
Hydroxypropyl methylcellulose 2910 (E-3)	10.00	10.00	10.00
Croscarmellose Sodium	3.00	3.00	3.00
Polyethylene Glycol 400	7.00	7.00	7.00
Acetone	410.00	410.00	410.00
Isopropyl Alcohol	610.00	610.00	610.00
Purified Water	10.00	10.00	10.00
COATING C			
Opadry 1	12.00	20.00	25.00
Purified Water	108.00	180.00	225.00

First, the core composition is prepared by placing zanamivir, sodium chloride, microcrystalline cellulose, hydroxypropyl methylcellulose 2208, polyethylene oxide and povidone in a high shear mixer and mix for 5 minutes. The granulation process is initiated by the gradual addition of a granulating solution containing polysorbate 20 and enough quantity of purified water to reach the granulation end point to the high shear with continuous blending to produce a wet blend. Next, the wet blend is granulated and dried at 40-50°C for 20 minutes in a fluid bed to remove the water. Then, the dry granules are screened through a 30 USP mesh screen for size reduction. Next, the screened granules are first mixed with the vitamin E TPGS, and then mixed with the colloidal silicon dioxide and the magnesium stearate that have been previously passed through a 60 mesh screen, in a V-Blender during 5 minutes. This final blend is tableted to provide the cores.

A first composition (semipermeable membrane) to cover the coated cores is prepared as follows: cellulose acetate and polyethylene glycol 400 are added to acetone

and mixed thoroughly to form a polymer solution. This solution is sprayed onto the tablets in a perforated pan coater to form semipermeable membrane coated cores. A 0.5 mm hole is drilled through the coating to provide perforated cores.

A second composition (drug-containing coat) to cover the perforated cores is prepared as follows: fexofenadine HCl, HPMC 2910, croscarmellose sodium, and polyethylene glycol 400 are added to the purified water, acetone and isopropyl alcohol to form the coating suspension. This suspension is sprayed onto the tablets in a perforated pan coater to obtain drug load coated tablets.

A finish coat comprising opadry in purified water is applied onto the film-coated tablets to obtain the multi-layered osmotic device tablets.

EXAMPLE 6

The following procedure is used to prepare a multi-layered osmotic device consisting essentially of zanamivir (200, 400 and 800 mg strength) in controlled release form in the core and loratadine (10 mg strength) in immediate/rapid release form in a drug-containing layer surrounding the coated core. The osmotic device made according to this procedure includes the following ingredients in the approximate amounts indicated.

Ingredient	Amount (mg)		
Zanamivir Strength⇒	200.00	400.00	800.00
Loratadine Strength⇒	10.00	10.00	10.00
CORE			
Zanamivir	200.00	400.00	800.00
Sodium Chloride	49.50	50.40	53.20
Polysorbate 20	1.00	1.50	2.00
Povidone	7.00	10.00	20.00
Hydroxypropyl methylcellulose 2208	5.00	6.00	10.00
Polyethylene Oxide 205 NF	35.00	42.00	49.00
Cellulose Microcrystalline	56.00	47.50	10.00
Vitamin E TPGS	36.60	39.00	43.80
Colloidal Silicon Dioxide	2.00	3.00	4.00
Magnesium Stearate	4.00	5.00	8.00
COATING A			
Cellulose Acetate 398	19.00	23.75	28.50
Polyethylene Glycol 400	1.00	1.25	1.50
Acetone	400.00	500.00	600.00
COATING B			

Ingredient	Amount (mg)		
Loratadine	10.00	10.00	10.00
Hydroxypropyl methylcellulose 2910 15 cps	24.00	24.00	24.00
Crospovidone	8.00	8.00	8.00
Polyethylene Glycol 6000	3.50	3.50	3.50
Colloidal Silicon Dioxide	0.50	0.50	0.50
Purified Water	540.00	540.00	540.00
COATING C			
Opadry 1	12.00	20.00	25.00
Purified Water	108.00	180.00	225.00

First, the core composition is prepared by placing zanamivir, sodium chloride, microcrystalline cellulose, hydroxypropyl methylcellulose 2208, polyethylene oxide 205 NF and povidone in a high shear mixer and mix for 5 minutes. The granulation process is initiated by the gradual addition of a granulating solution containing polysorbate 20 and enough quantity of purified water to reach the granulation end point to the high shear with continuous blending to produce a wet blend. Next, the wet blend is granulated and dried at 40-50°C for 20 minutes in a fluid bed to remove the water. Then, the dry granules are screened through a 30 USP mesh screen for size reduction. Next, the screened granules are first mixed with the vitamin E TPGS, and then mixed with the colloidal silicon dioxide and the magnesium stearate, that have been previously passed through a 60 mesh screen, in a V-Blender during 5 minutes. This final blend is tabletted to provide the cores.

A first composition to cover the coated cores is prepared as follows: cellulose acetate and polyethylene glycol 400 are added to acetone and mixed thoroughly to form a polymer solution. This solution is sprayed onto the tablets in a perforated pan coater to form semipermeable membrane coated cores. A 0.5 mm hole is drilled through the coating to provide perforated cores.

A second composition to cover the perforated cores is prepared as follows: loratadine, HPMC 2910, crospovidone, and polyethylene glycol 6000 are added to the purified water to form the coating suspension. This suspension is sprayed onto the tablets in a perforated pan coater to obtain drug load coated tablets.

A finish coat comprising opadry in purified water is applied onto the film-coated tablets to obtain the multi-layered osmotic device tablets.

The above is a detailed description of particular embodiments of the invention. It is recognized that departures from the disclosed embodiments may be made within the scope of the invention and that obvious modifications will occur to a person skilled in the art. Those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed herein and still obtain a like or similar result without departing from the spirit and scope of the invention. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.